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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/266,803 | 03/12/99 | GLENN G | PM-256865 |

HM12/1207

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| EXAMINER | |
|---|---|
| TUNG, M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 14 |

**DATE MAILED:** 12/07/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/266,803 | Glenn And Alving |
| **Examiner** | **Group Art Unit** |
| Mary B. Tung | 1644 |

☒ Responsive to communication(s) filed on *5/9 and 9/20/2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

☒ Claim(s) *1-40* is/are pending in the applicat

Of the above, claim(s) *13-15, 25, 26, and 36-40* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 16-24, and 27-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-40* are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *1, 5, 6, 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

***--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---***

## *DETAILED ACTION*

1. The Associate Power of Attorney, filed 2/18/00, Paper No. 7, has not been properly signed and has not been entered. A person acting in a representative capacity without power of attorney may not sign a Power of Attorney, see MPEP § 402.

### *Election/Restriction*

2. Applicant's election without traverse, of the species of enhancers :chemical, antigen: pathogen, and adjuvant: ADP ribosylating exotoxin, readable on claims 1-12, 16-24 and 27-35 in the paper filed September 20, 2000, Paper No. 13 is acknowledged.

3. Claims 13-15, 25, 26 and 36-40 are patentably distinct and are accordingly held to be withdrawn from further consideration under 37 C.F.R. 1.142(b).

4. The requirement is still deemed proper and is therefore made FINAL.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with *37 C.F.R. § 1.48(b)* if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under *37 C.F.R. § 1.48(b)* and by the fee required under *37 C.F.R. § 1.17(h)*.

### *DECLARATION*

6. The oath or declaration is defective. A new oath or declaration in compliance with *37 C.F.R. § 1.67(a)* identifying this application by its Serial Number and filing date is required. *See M.P.E.P. §§ 602.01* and *602.02*.

7. The oath or declaration is defective because:

8. It appears that there are non-initialed alterations made to the oath or declaration to the Post Office Address of Inventor Glenn (*see 37 C.F.R. §§ 1.52(c) and 1.57*). The quality of the faxed copy of the oath renders it very difficult to read.

Title

9. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Method of Inducing an Immune Response Using an Adjuvant for Transcutaneous Immunization".

*Information Disclosure Statement*

10. The references WR, XR, ZR, AAR and DDR listed on the form PTO-1449 filed Dec. 28, 1999 have no publication dates. Applicant is required to supply the publication dates of these references.

*Claim Rejections - 35 U.S.C. § 112*

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

12. Claims 4 and 5 are rejected under *35 U.S.C. § 112*, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

13. Claim 4 lacks an antecedent basis in the recitation of "physical, chemical electrical or sonic penetration enhancer".

14. Claim 4 appears to be an incomplete sentence.

15. Claim 5 lacks an antecedent basis in the recitation of "allergic reaction".

16. Claim 6 lacks an antecedent basis in the recitation of "applying alcohol to the intact skin prior to application of the formulation".

*Claim Rejections - 35 U.S.C. § 102*

17. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-4, 7-12, 18-21, 30 and 21-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Domb (US Patent #5,340,588).

19. The '588 patent teaches a method of inducing an immune response to an antigen (see col. 2, lines 9-12, in particular), by applying a formulation to intact skin of an organism, wherein the formulation comprises liposomes and the antigen, as recited in claims 3 and 14 (see col. 2, lines 20-26, in particular) and wherein the formulation further contains an adjuvant (see col. 6, lines 41-51, in particular), as recited in claims 1-3, inducing the immune response in the organism wherein the immune response is specific for the antigen (see col. 8, lines 12-16, in particular), an antigen, R32NS1, that has a molecular weight or greater than 800 Daltons, as recited in claims 10 and 16 ((209 amino acids, approximately 22,990 Daltons) see col. 21, line 46, in particular), and wherein the antigen is derived from a pathogenic bacteria as recited in claim 12. Claim 4 is included because the Applicants disclose on page 20, lines 31-33 that lipids are penetration enhancers. Claims 7-9, 18-21 and 32-35 are included because the immune response invoked would be an inherent property of the claimed method. Therefore, the reference teaching anticipates the claimed invention.

### *Claim Rejections - 35 U.S.C. § 103*

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1-12, 16-23 and 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domb (US Patent #5,340,588) or alternatively over Paul, et al. *(YR; Eu. J. Immunol. 25:3521-3524, 1995)*, and further in view of Marinaro, et al. *(J. Immunol. 155:4621-4629, 1995)* and the admitted prior art on page 16, lines 23-25 and 33.

23. The '588 patent has been discussed, *supra*. Paul, et al. (YR) teaches a method of inducing an antigen-specific non-allergic immune response by transdermal immunization of intact skin comprising an antigen gap junction protein, derived from a normal cell, as recited in claim 11 and greater than 750 Da, as recited in claims 10 and 16, or BSA; see pages 3521 and 3522 and the abstract, in particular) and liposomes (as recited in claim 3), The claimed invention differs from the reference teaching only by the recitation of a the inclusion of the ADP-ribosylating exotoxin, cholera toxin or cholera toxin B subunit. However, Marinaro, et al. teaches that cholera toxin has become a model mucosal immunogen and adjuvant because microgram quantities of cholera toxin induces significant serum IgG antibodies and these responses are major histocompatability complex restricted (see page 4621, col 1, paragraph 1 and bridging over to page 4622, col. 1, paragraph 2, in particular) and the Applicant admits as prior art on page 16, lines 23-25 and 33 that cholera toxin is known to be an adjuvant. To provide a composition to effect or enhance immunization of an animal against an antigen, one of ordinary skill in the art at the time the invention was made would have been motivated to use cholera toxin as an adjuvant in the composition taught in the '588 patent, in order to provide an major histocompatability complex restricted IgG antibody response to the desired antigen. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. The identification of cholera toxin as an ADP-ribosylating exotoxin was admitted by the Applicant on page 16, lines 3-7, 12 and 13 of the specification. Claim 4 is included because the Applicants disclose on page 20, lines 31-33 that lipids are penetration enhancers. Claim 6 is included because it would be obvious to clean the skin prior to administration of the antigen, with alcohol. Claims 7-9, 18-21 and 32-35 are included because the immune response invoked would be a characteristic outcome of the claimed method. Claim 17 is included because it is well known to one of ordinary skill in the art to make use a multivalent antigen, as recited in claim 17, in order to make a vaccine to several antigens at once.

24. Claims 1-12, 16-24 and 27-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domb (US Patent #5,340,588) or alternatively over Paul, et al. *(YR; Eu. J. Immunol. 25:3521-3524, 1995)*, in view of Kosecka *(Am. J. Physiol. 267 (Gastrointest. Liver Physiol. 30):G745-G753, 1994)* and the admitted prior art on page 16, lines 3-7, 23-25 and line 33 and in further view of Wille, et al. (US Patent No. 5,686,100).

25. The '588 patent and Paul (YR) have been discussed, *supra*. The claimed invention differs from the reference teaching only by the recitation of a the inclusion of the E. coli heat-labile enterotoxin or pertussis toxin and an occlusive dressing, as recited in

claim 28. However, Kosecka, et al. teaches that pertussis toxin enhances nerve-mediated uptake in intestines (see the title, in particular). Additionally the Applicant discloses as known in the art, that cholera toxin is an ADP-ribosylating exotoxin (reviewed by Craggier and Barbieri, 1995, see page 16, line 33 of the specification) and the cholera toxin and its subunit have adjuvant properties when used as either an intramuscular or oral immunogen (see lines 23-25 of the specification). The '100 patent teaches a patch for the transcutaneous or transdermal delivery of drugs that comprises a protein antigen, as recited in claim 16 (see col. 6, lines 29 (urokinase)), wherein the composition includes a gel or ointment, as recited in claim 27 (see col. 7, lines 33-40) and an occlusive dressing (see col. 1, line 62 and bridging over to col. 2, line 18, in particular). The local sweat retention syndrome resulting from prolonged skin occlusion (see col. 2, lines 17-19) would innately be due to the "backing" taught in col. 2, line 3, being occlusive in nature. To provide a composition to effect or enhance immunization of an animal against an antigen, one of ordinary skill in the art at the time the invention was made would have been motivated to use pertussis toxin as an adjuvant in the composition taught in the '588 patent, or cholera toxin, as disclosed as a known in the art, in the patch composition taught by the '100 patent in order to provide an immune response to the desired antigen. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. Claim 4 is included because the Applicants disclose on page 20, lines 31-33 that lipids are penetration enhancers. Claim 6 is included because it would be obvious to clean the skin prior to administration of the antigen, with alcohol. Claims 7-9, 18-21 and 32-35 are included because the immune response invoked would be a characteristic outcome of the claimed method. Claim 17 is included because it is well known to one of ordinary skill in the art to make use a multivalent antigen, as recited in claim 17, in order to make a vaccine to several antigens at once.

***Double Patenting***

26. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

27. A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b).

28. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

29. Claims 1-4, 6-12, 16-21, 27-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 and 15-29 of US Patent No. 5,910,306, in view of Unger (US Patent #5,733,572) and in further view of Albert (US Patent #5,256,422).

30. The claimed invention of the instant application differs from the '306 patent in that the claim 1 of the '306 patent recites a method of inducing an immune response comprising applying a formulation to intact skin of an organism, whereby the formulation comprises an antigen, as recited in claim 1 of the instant application, or a liposome (see claim 3 of the instant application), wherein the antigen is derived from a bacterial pathogen (see claims 11 and 12 of the '306 patent and claims 11 and 12 of the instant application, and contains an adjuvant (see claim 28 of the '306 patent). Claims 2-9 and 29 of the '306 patent are mechanisms which lend no patentable weight to the claims; claims 16 and 17 of the '306 patent are product by process claims which do not materially affect the properties of the product and thus lend no patentable weight to the claims. Claims 10 and 18 of the '306 patent encompass claims 10 and 16 of the instant application, wherein the claims of the '306 patent are "greater than 500 daltons". Claim 4 of the instant application is included because the Applicants disclose on page 20, lines 31-33 that lipids are penetration enhancers. Claim 6 of the instant application is included because it would be obvious to clean the skin prior to administration of the antigen, with alcohol. Claims 7-9, 18-21 and 32-35 of the instant application are included because the immune response invoked would be a characteristic outcome of the claimed method. Claim 17 of the instant application is included because it is well known to one of ordinary skill in the art to make use a multivalent antigen, as recited in claim 17, in order to make a vaccine to several antigens at once.

31. The claimed invention in claims 18-27 of the '306 patent differs from the claims of the instant application only by the recitation of a method wherein the liposomes are unilamellar, paucilamellar, or multilamellar, formed from phospholipid, and/or sterol, wherein the phospholipids are selected from the group consisting of phosphatidylcholine, phosphatidyl glycerol, etc, and mixtures thereof, wherein the sterol is cholesterol, wherein the liposomes are formed from a non-ionic amphiphile

selected form the group consisting of polyoxyethylene fatty acid ester, and so forth, and wherein the liposome is formed from an ionic amphiphile selected from the group consisting of betaine, sarcosinic acid, and so forth. To provide a method for the topical delivery of an active ingredient (including drugs, peptides and bioactive compounds) to a selected tissue of a patient (see col. 6, lines 25-30, in particular), the '572 patent teaches liposomes which are unilamellar or multilamellar or oligolamellar (see col. 5, lines 5-58, in particular), formed from phospholipids selected from the group consisting of phosphatidylcholine, phosphatidylglycerol, phosphatidylserine, phosphatic acid, phosphatidylinositol, lysophosphatide, sphingomyelin, and mixture thereof ('572, see col. 14, lines 55 and bridging over to col. 15, line 56, in particular), wherein the sterol comprises cholesterol (see col. 14, lines 51-54, col. 15, lines 7 and 8, and col. 16, lines 9-28, in particular) and wherein the liposomes are formed from an ionic amphiphile to provide stability to the liposome (see col. 14, lines 22-42 and claim 22, in particular). To form lipid vesicles, the 422 patent teaches the liposomes which are paucilamellar ('422, see col.3, lines 25-29, in particular), and wherein the liposomes are formed from a nonionic amphiphile selected from the group consisting of polyoxyethylene fatty acid ester, polyoxyethylene fatty acid ethers, diethanolamides, long chain acyl hexosamides, long chain acyl amino amides, long chain amino acid amines, polyoxyethylene sorbitan esters, polyoxyethylene glyceryl mono- and diesters, glycerol mono- and distearate, glycerol mono- and dioleate, glycerol mono- and dipalmitate, and mixtures thereof ('422, col. 2, lines 57-65, in particular). One of ordinary skill in the art at the time the invention was made would have been motivated to include the various lipids and sterols taught by the '572 and 422 patents in the liposomes of the instant application, since these compounds are known in the art to be useful in preparing liposomes and stabilized microspheres (see the '572 patent, col. 13, lines 13-44, in particular).

### *Conclusion*

32. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

33. Papers related to this application may be submitted to Group 1640 by facsimile transmission. Papers should be faxed to Group 1640 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). THE CM1 FAX CENTER TELEPHONE NUMBER IS (703) 305-3014 or (703) 308-4242.

34. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mary Tung whose telephone number is (703)308-9344.

The Examiner can normally be reached Tuesday through Friday from 8:30 am to 6:00 pm and on alternating Mondays. A message may be left on the Examiner's voice mail service. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1640 receptionist whose telephone number is (703) 308-0196.

December 5, 2000
Mary B. Tung, Ph.D.
Patent Examiner
Group 1640

Mary Beth Tung

MARY BETH TUNG, PH.D
PATENT EXAMINER